REMARKS/ARGUMENTS

The Status of the Claims.

Claims 1, 11-12, 20-21, 24-26, and 74-75 are pending with entry of this response, claims 6, 13, 18, 19, and 73 being cancelled herein and claims 74 and 75 being added. Claims 1, 11, 12, and 20 are amended herein. These amendments are fully supported throughout the specification as filed, e.g., in the original claims. Therefore, no new matter is added and Applicants respectfully request that the amendments be entered.

Interview Summary

Date of interview: February 2, 2010
Type: Telephonic
Claims discussed: all pending
Prior art discussed: all pending
Participants:

Cherie Woodward, Examiner,
Gary Nickol, SPE,
Christopher Hunter, Applicant
Stacy Landry, Applicants' undersigned attorney

Summary of discussion

1. Applicants briefly related the prosecution history of the case.
2. The cited prior art was discussed. Applicants' undersigned attorney indicated that the cited prior art documents teach that IL-27 should be used to activate the immune system. The following particular quotes from Timans were discussed.

> Paragraph 39:
> "IL-D80 or IL-27 agonists, or antagonists, may also act as functional or receptor antagonists. Thus, IL-D80, IL-27, WSX-1/TCCR, or its antagonists, may be useful in the treatment of abnormal medical conditions, including immune disorders, e.g., T cell immune deficiencies, inflammation, or tissue rejection, or in cardiovascular or neurophysiological conditions."
>
> Paragraph 161
> "Taken together the above indicates a role for the composite cytokine and its associated receptor subunit WSX-1/TCCR in inflammatory responses. Therefore antagonizing the function of any of the components in the receptor subunit:ligand complex should have a beneficial effect in inflammatory diseases, e.g., inflammatory bowel disease, rheumatoid arthritis, etc."

Applicants and the Office disagreed on the meaning of the above quotes. Applicant's undersigned attorney stressed that the reference must be read as a whole. Dr. Hunter respectfully stated that he thought the quotations were taken out of context by the

Examiner and that later publications by the same authors support Applicants' interpretation of what is taught by the cited documents. *See, e.g.*, Chen, Q., N. Ghilardi, H. Wang, T. Baker, M. H. Xie, A. Gurney, I. S. Grewal, and F. J. de Sauvage. (2000). Development of Th1-type immune responses requires the type I cytokine receptor TCCR. *Nature* 407:916-920; Yoshida, H., S. Hamano, G. Senaldi, T. Covey, R. Faggioni, S. Mu, M. Xia, A. C. Wakeham, H. Nishina, J. Potter, C. J. Saris, and T. W. Mak. (2001). WSX-1 is required for the initiation of Th1 responses and resistance to L. major infection. *Immunity* 15:569-578; and Pflanz, S., Timans, J. C., Cheung, J., Rosales, R., Kanzler, H., Gilbert, J., Hibbert, L., Churakova, T., Travis, M., Vaisberg, E., Blumenschein, W. M., Mattson, J. D., Wagner, J. L., To, W., Zurawski, S., McClanahan, T. K., Gorman, D. M., Bazan, J. F., de Waal Malefyt, R., Rennick, D., Kastelein, R. A. (2002). IL-27, a heterodimeric cytokine composed of EBI3 and p28 protein, induces proliferation of naive CD4(+) T cells. *Immunity* 16:779-790. This discussion focused in part on what is meant by "immune suppression" and what patient population is being treated. Dr. Hunter gave the example of people in need of immune suppression as those being treated with steroids and stressed that this was only an example. Examiner Nickol indicated that he might reconsider the claims if the patient population were more clearly defined.

3. Applicants' undersigned attorney then described the state of the art at the time of Applicants' invention, which led to a discussion of the date of Applicants' invention. Applicants' undersigned attorney stated that, at this point and for this purpose only, the date used could be set, *arguendo*, as the filing date of the present application, although Applicants maintain that the priority date should be January 31, 2003, as claimed. Applicants' undersigned attorney stressed that even at the time of filing, which is later than Applicants' actual invention, the state of the art was that IL-27 should be used to activate the immune system, not suppress it as claimed. Examiner Woodward also expressed some skepticism regarding whether Applicants' invention actually works, to which Dr. Hunter responded with a description of subsequent work supporting Applicants' original claims.

4. Because Applicants were not accorded the priority date of the provisional applications filed January 31, 2003 and November 10, 2003 due to alleged lack of correspondence with claim scope, Applicants requested that the priority be reconsidered in light of claim amendments made on 5/25/2007 and 12/10/2007. Examiner Woodward indicated that her issue with the priority document is enablement. Applicants' undersigned attorney stated that the rejection had not been clearly stated and that Applicants would appreciate a more thorough explanation of the rejection in light of claim amendments. Examiner Woodward agreed to provide a detailed explanation.
5. Applicants' undersigned attorney described and quoted from post filing reviews of the art to illustrate that Applicants' invention was not anticipated. Applicants's undersigned attorney called attention to recent reviews, such as Batten 2007 (reference #28 in Appendix) which refers, on page 665, to Applicants' results as "striking" and "unexpected"; Kastelein 2007 (reference #29 in Appendix) which refers, on page 233, to Applicants' "unexpected insights into the role of this cytokine in limiting inflammation," and Yoshida 2009 (reference #34 in Appendix) referring, in the abstract, to IL-27 as unique in that it induces Th1 differentiation and suppresses immune responses.
6. Whether a new use of a known compound is patentable was also briefly discussed. Examiner Woodward stated that such subject matter is only marginally patentable. Anticipation by inherency was also discussed. Applicants' undersigned attorney pointed out that both of these issues were addressed extensively in Applicants' response filed August 8, 2008. In summary, the Office held to its assertion that the claims are anticipated under 35 U.S.C. § 102.

Information Disclosure Statement

Applicants submit herewith an Information Disclosure Statement citing references discussed in the interview and references cited in the review of IL-27 research provided herein.

Priority Claims

Benefit of the filing dates of provisional application 60/444,494, filed January 31, 2003, and provisional application 60/519,074, filed November 10, 2003, was not acknowledged by the Examiner. As described in detail in the response filed December 10, 2007 and in the response filed August 8, 2008, Applicants have presented a proper priority claim to both documents and respectfully request that priority be accorded.

Furthermore, Applicants respectfully request that the refusal to accord priority be reconsidered in light of amendments 5/25/2007 and 12/10/2007. Priority was not accorded because the priority documents were alleged to not correspond to the breadth of the claims. See, Office Action mailed 11/29/2006.

Prosecution History

In the first round of prosecution (Office Action mailed 11/29/2006; response filed 5.25.2007), Applicants responded to 35 U.S.C. § 102 rejections with a brief description of the prior art as a whole, explaining that the prior art teaches exactly the opposite of what Applicants' claim.

In the second round of prosecution (Office Action mailed 8/9/2007; response filed 12/10/2007), Applicants arguments regarding the prior art were deemed unpersuasive and Applicants responded with detailed review of cited art, including the full quotations on which the Office relied.

In the third round of prosecution (Office Action mailed 2/26/2008; response filed 8/8/2008), an interview was conducted with Examiner Woodward, Dr. Chris Hunter and Dr. Stacy Landry. Dr. Hunter and Dr. Landry came away from the interview believing that Examiner Woodward acknowledged the differences between the prior art and the claimed invention, but was still unsure whether the claims were patentable as a new use of a known compound and under the inherency doctrine. Applicants therefore provided, in their response, a general review of anticipation by inherency and explained why it could not be applied to this case, e.g., because the selection of the claimed patient population is not inherent or explicit in the prior art. Applicants also provided a general review of the law

regarding patentability of a new use of a known compound to show that Applicants' claims are patentable as such.

In the fourth round of prosecution (Office Action mailed 11/21/2008; response filed 8/21/2009), Applicants' arguments regarding a new use of a known compound were rejected as too general to be applicable to the cytokine at issue and arguments regarding pleiotrophic qualities of cytokines were put forward. Applicants arguments addressed the use of the extrinsic evidence and pointed out that no amount of extrinsic evidence could overcome the defects in the prior art rejection. The cited prior art simply does not teach the use that Applicants' claim for IL-27 and other IL-27R agonists. Applicants also objected to The Office's attempt to use Applicants' priority document against them in a 35 U.S.C. § 102 rejection. These arguments did not overcome the rejections and Applicants proceeded to the Examiner interview described above and the present response.

State of the Art regarding IL-27 and IL-27R prior to and subsequent to Applicants' application for a patent.

The following is a narrative outlining critical publications that first described the role of the IL-27R (WSX-1/TCCR) in promoting inflammation, the description of IL-27 (composed of p28 and EBI3) and the initial description of the EBI3 KO mice. Also provided are references form independent sources that summarize the consensus of those of skill in the art at various times on the biology of IL-27. Numbered references are provided in the attached Appendix and submitted with the IDS filed herewith.

1. IL-27R (WSX-1) was cloned and identified as a type I cytokine receptor and postulated to have a role in the immune system (1).

2. EBI3 was cloned (2), proposed to form a heterodimer with IL-12 p35 (3)(to form what is now known as IL-35) and knocked out(4). Mice were reported to be resistant to oxazolone induced colitis and had reduced production of TH1 (IFN-g) and TH2 (IL-4) cytokines. Also reported, was a developmental defect in invariant NKT cells –this was suggested to provide an explanation for the lack of disease as these iNKT cells contribute

to this model of oxazalone-induced inflammation. These data provided the first indication that EBI3 was required for inflammatory responses.

3. The first KO of the IL-27R is reported by a research group from Genentech headed by Fred Desauvage and which contained Nico Ghilardi(5). In this manuscript they presented data that the TCCR (IL-27R) deficient mice had a defect in the ability to produce IFN and consistent with this observation these mice were more susceptible to infection with Listeria. This led the authors to conclude that their "results demonstrate the existence of a new cytokine receptor involved in regulating the adaptive immune response and critical to the generation of a Th1 response". The apparent specificity of the phenotype described here makes TCCR and its potential ligand candidate targets for therapeutic intervention in Th1-mediated autoimmune disease and allograft rejection.

4. Studies from Hiroki Yoshida in the laboratory of Tak Mak in Toronto were published in Immunity in 2001 and showed that WSX-1 (IL-27R) KO mice were more susceptible to infection with the parasite Leishmania(6). These data were consistent with reduced production of IFN-g in these mice and the authors concluded that "WSX-1 is essential for the initial mounting of Th1 responses"

5. In 2002, studies from the laboratory of Robert Kastelein at DNAX revealed that WSX-1 was a receptor for a novel cytokine composed of p28 and EBI3 which they called IL-27(7). In that manuscript they showed that IL-27 could promote the production of IFN-g from NK and T cells.

6. At this point, a consensus was emerging that IL-27, and signaling through its receptor, was an important step in the generation of Th1 responses. This idea is highlighted in several reviews that were published at the time by independent experts in the field. For example Robinson and O'Garra (8) concluded that "IL-27 appears to act at an early stage in Th1 development in a manner distinct from IL-12". In that same year, two leading experts in the field of T cell differentiation, Ken Murphy and Steve Reiner, summarized the state of the field in their review article in *Nature Reviews Immunology*(9). In that review they have a section devoted to "Recently discovered T_H1-cell-promoting factors"

and highlight the role of IL-27 in these events. In Figure 8 of that article, they clearly place IL-27 as a factor that promotes the early differentiation of Th1 cells. Similarly Brombacher and colleagues in a review article concluded that "IL-27 is involved in early Th1 initiation" (10). In 2003 there were three additional publications that reinforced the concept that IL-27 promoted TH1 responses from the groups at Genentech, DNAX and Hiroki Yoshida (11-13). Articles in 2004/2005 (14, 15) continued to highlight the ability of IL-27 to promote the production of IFN-g without mention of any anti-inflammatory effects.

7. Based on this literature one of skill in the art would blockade IL-27R to reduce Th1 responses and enhance signaling through IL-27R to increase Th1 responses. In other words, these studies implicitly implied that neutralization of IL-27 or its receptor would be a viable strategy to prevent or ameliorate pathology caused by Th1 type responses, for instance in the setting of autoimmunity or transplantation. Alternatively, they implied that using IL-27 or promoting signaling through its receptor could be used to *augment* inflammatory responses; for example during vaccination or cancer therapy. This use of IL-27 is exactly the opposite of that claimed, i.e., "selecting a patient *with immune hyperactivity*; and . . . administering to said patient an effective amount of an IL-27R *agonist*" (Claim 1; emphasis added).

8. In 2002, Applicants obtained IL-27R deficient mice from Amgen to determine whether IL-27R was required for the development of protective immunity to the pathogen Toxoplasma gondii. Immunity to this organism is dependent on the ability to produce IFN-g and based on the then existing dogma, Applicants postulated that, in the absence of the IL-27R, mice would be unable to mount a protective inflammatory response characterized by the production of IFN-g. Applicants' studies with the IL-27R KO mice demonstrated that, contrary to all expectations, when infected with *T. gondii*, the mice developed a hyper-inflammatory response characterized by excessive production of IFN-g (and other cytokines) and that the CD4+ T cells in these mice mediated disease. These studies were published in Immunity in late 2003(16) almost a year after the initial provisional patent filing. These studies were accompanied by a manuscript from our

collaborator, Hiroki Yoshida, that reached a similar conclusion with a different pathogen (17).

9. The finding that the IL-27R was in fact required to dampen inflammatory responses was regarded as extremely novel and was highlighted in an accompanying commentary article(18), by authors associated with Schering Plough/DNAX. In that article they noted that "These data suggest that IL-27 not only is dispensable for the generation of Th1 responses in strongly polarizing conditions, but, likely due to its ability to activate STAT1 and 3, also exerts a powerful negative feedback mechanism that limits T cell hyperactivity and IFN-γ production."

10. In contrast to the dogma at the time, the finding that the IL-27R was required to limit immune hyperactivity implied that IL-27 or promoting signaling through the IL-27R would be a useful way to turn off inflammation. Alternatively, the neutralization of IL-27 or blocking signaling through the IL-27R might be a useful way to augment immune responses. These key conclusions are the exact opposite of the conclusions provided in paragraph 7 above. Subsequent studies since 2004 have provided ample independent examples of situations where IL-27 is a potent antagonist of inflammatory responses(19-26). Rather than listing all of these examples there are multiple reviews and commentaries that highlight the anti-inflammatory properties of IL-27 and its potential use as a therapeutic to block inflammation (27-35).

11. Applicants do not disagree with the initial conclusion that, under certain circumstances, IL-27 may promote inflammatory responses and there is an established literature on this facet of IL-27 biology. Rather, we would contend that the observation that the IL-27R was actually a potent inhibitor of inflammation was unexpected and would not have been predicted based on the pre-existing literature in 2003.

The claims are not anticipated under 35 U.S.C. §102.

Claims 1, 6, 11-13, 18-21, 24-26, and 73 were rejected under 35 U.S.C. §§102(a) and 102(e) as allegedly anticipated by Timans et al.; under 35 U.S.C. §102(b) as

allegedly anticipated by De Sauvage et al. and by Bennet at al.; and under 35 U.S.C. §102(e) as allegedly anticipated by Matthews et al. Applicants respectfully traverse each rejection as provided in the responses filed December 10, 2007, August 8, 2008, and August 21, 2009 and for the reasons provided herein.

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention. Anticipation requires that "all limitations of the claim are found in the reference, or 'fully met' by it." Kalman v. Kimberly-Clark Corp., 218 USPQ 781, 789 (Fed. Cir. 1983).

Work prior to Applicants provisional and/or utility patent filing date indicated that one of skill in the art would have used IL-27 (and IL-27R agonists) to activate the immune system. For example, Chen 2000 (5) states that development of a Th1 immune response requires IL-27R. Yoshida 2001 (6) indicates that IL-27R is required for Th1 response. Pflanz 2002 (7) states that IL-27 induces proliferation of T cells. In addition, numerous review articles (8-15) support the assertion that at the time of Applicants invention, the consensus view was that IL-27 was required for immune activation. This is exactly the opposite of what is being claimed.

In addition, the review accompanying publication of Applicants' work also explains that the work contradicts the general consensus about this particular cytokine (18). (See, Trinchieri, G., S. Pflanz, and R. A. Kastelein. 2003. The IL-12 family of heterodimeric cytokines: new players in the regulation of T cell responses. *Immunity* 19:641-644, page 643, last 10 lines at the bottom of second column.)

Review articles published subsequent to Applicants' filing date are consistent in the view that IL-27 was considered an immune activator prior to Applicants' work and that the claim to using it as an immune suppressant is new and unexpected. For example, Batten 2007 (28) refers, on page 665, to Applicants' results as "striking" and "unexpected". Kastelein 2007 (29) refers, on page 233, to the "unexpected insights into the role of this cytokine in limiting inflammation." Yoshida 2009 (34) refers, in the abstract, to IL-27 as unique in that it induces Th1 differentiation and suppresses immune responses. Therefore, a

complete review of the art in its entirety clearly indicates that Applicants' work and the claimed invention are novel over the art.

Additional arguments presented by the Examiner in the most recent Office action have yet to show where, in the prior art (or in the state of the art generally at the time of the invention or the time of filing), a patient in need of immune suppression, e.g., a patient experiencing immune hyperactivity, as presently claimed, was explicitly or inherently selected for and administered an IL-27R agonist. Applicants' claims are therefore a novel, patentable new use for a known compound.

Applicants note that in interviews the Office has expressed concern with inherency and patentability of a new use for a known compound but has not addressed these issues or Applicants' response thereto in writing.

Applicants have shown in prior responses and herein why Applicants' claimed methods are a patentable new use of a known compound and respectfully request that all of the rejections under 35 U.S.C. § 102 be withdrawn.

Non-Statutory Obvious-Type Double Patenting

Claims 1, 6, 11-13, 18-23, and 73 were provisionally rejected for alleged non-statutory obvious-type double patenting over claims 21-24 and 26-28 of co-pending application 11/880,121. The Examiner requested that a terminal disclaimer be filed under 37 C.F.R. § 1.321(c) or (d). When all substantive issues have been resolved and the claims are otherwise in condition for allowance, Applicants will submit a terminal disclaimer over the claims of USSN 11/880,121 if it is still necessary at that time.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

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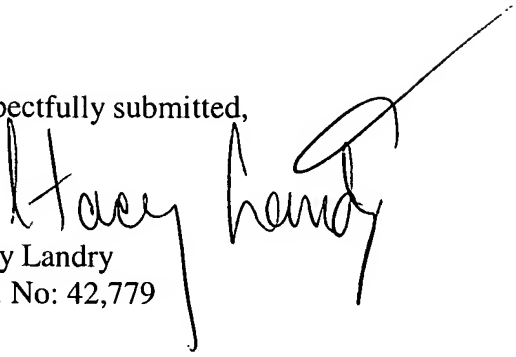
Respectfully submitted,



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Appendix

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